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Gender Differences in Susceptibility of Asthma to Active Smoking —Questionnaire Based Analysis in the Niigata Prefecture, Japan—

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ABSTRACT

Background: The importance of smoking in bronchial asthma has been thoroughly investigated. Although a high smoking rate has been recognized in Japan, there have been few studies of the relationship between active smoking and bronchial asthma, and little analysis of the gender difference in this relationship. The aims of this study were to examine the contribution of active smoking to asthma and to clarify any gender difference.

Methods: For 8 weeks from September through October 2000, a smoking questionnaire survey was performed on adult patients with bronchial asthma, and their attending physicians, in Niigata Prefecture, Japan. The questionnaire surveyed asthma control, asthma-related emergencies and satisfaction in daily life. The attending physicians were questioned about patient profiles and medications. Patients were classified into three groups : non-smokers (NS), ex-smokers (ES) and current smokers (CS). For examination of gender differences, the CS group was compared with the NS group, due to variable duration of smoking and of cessation of smoking in the ES group.

Results: Complete data were received from 2947 cases. Of the male patients, 340 (23.0%) were in the CS group, 325 (22.0%) were in the NS group and 812 were in the ES group. Of the female patients, 109 (7.4%) were in the CS group, 1132 (77.4%) were in the NS group, and 229 (7.4%) were in the ES group. The male CS group had more severe asthma-related symptoms in the morning and at night, more sputum and cough in the morning, and more severe sleep disturbance than the male NS group. In the female patients, these differences were not detected. A logistic and multiple regression analysis confirmed these significant differences between male and female asthma patients.

Conclusions: The gender differences in the susceptibility of asthma to smoking suggests the need for gender-specific strategies for smoking cessation, although further investigation is required.

KEY WORDS

active smoking, asthmatic symptoms, gender difference, susceptibility

INTRODUCTION

Active cigarette smoking is common in adult asthma patients, and their prevalence rates are likely to be similar to the general population.[1] The current smoking rate among asthma patients ranges from 17% to 35%.[2-9] Because the pathogeneses of bronchial asthma is thought to be inflammation of the bronchi that leads to bronchial hypersensitivity and bronchial airflow limitation,[10] the influence of smoking was

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Table 1 Contents of the questionnaire used for asthmatic patients in this study (originally in Japanese.)

Age: years old	Gender: male/female
Question 1	
When were you first diagnosed as having bronchial asthma?	Year: Month: Day:
Question 2	
1) Choose one of the following to describe your smoking (non-smoker, ex-smoker, current smoker)	
2) For ex-smokers, please answer the followings:	
How old were you when you started smoking?	Your starting age:
How old were you when you stopped smoking?	Your stopping age:
How many cigarettes did you smoke per day?	Cigarettes/day (mean):
Was stopping smoking related to your asthma?	Yes or No:
3) For current smokers, please answer the following:	
How old were you when you started smoking?	Your starting age:
How many cigarettes did you smoke per day?	Cigarettes/day (mean):
Question 3	
1) Do you use a peak-flow meter?	(Yes, No)
2) What was the average value of your peak-flow meter during the last 2 weeks?	
morning:	night:
Question 4 Select one answer to each of the following questions:	
1) How often did you have asthma attacks during the last 12 months? (frequent attacks, seasonal attacks, few attacks)	
2) How often did you have asthma attacks during the last 2 weeks? (5–7/week, 3–4/week, 1–2/week, non)	
3) How severe were your asthma attacks during the last 2 weeks? (impossible to move, impossible to lie down, possible to lie down, stridor, breathless on exertion)	
4) Have you ever been hospitalized due to asthma? (Yes, No)	
5) Have you ever been taken by ambulance or visited an emergency room due to an asthma attack? (Yes, No)	
6) Have you ever been placed on a respirator due to an asthma attack? (Yes, No)	
7) Have you ever been unconscious during an asthma attack? (Yes, No)	
8) Have you ever had an attack induced by anti-inflammatory drugs including painkillers, antipyretics, or cold medicine? (Yes, No)	
Question 5 How bad was your asthma during the last 2 weeks? (very good, fairly good, mediocre, slightly bad, bad)	
Question 6 Describe your symptoms during the last 2 weeks:	
1) in the morning (cough, sputum, chest tightness, stridor, dyspnea, no symptoms)	
2) at night (cough, sputum, chest tightness, stridor, dyspnea, no symptoms)	
3) sleep disturbance (sometimes cannot fall asleep due to dyspnea, cannot to have a good sleep due to dyspnea, waking up in the night due to chest tightness, none)	
Question 7	
Are you satisfied in daily life? (very satisfied, fairly satisfied, mediocre, slightly unsatisfied, not satisfied)	

brought to the attentions of these asthmatic stages.[11-13] The influence of smoking on the therapeutic response to corticosteroids has been reported.[14] However, it is important to study the clinical implications of active smoking, and few such studies have been performed in Japan.

It is well known that disease profiles and factors associated with diseases can vary by sex. In respiratory

Table 2 Adult bronchial asthma severity assessment committee's standards of the Japanese Society of Allergology

frequency	Severity of symptoms			
	A	B	C	D (D1/D2)
5–7/week	severe	severe	moderate	moderate
3–4/week	severe	moderate	moderate	mild
1–2/week	severe	moderate	mild	mild

A: impossible to move due to dyspnea, B: impossible to lie down due to dyspnea, C: possible to lie down even with dyspnea, D1: stridor alone, D2: chest tightness alone

diseases, gender differences of the bronchi have been reported.[15] Although cigarette smoking is thought to cause more respiratory symptoms and greater deterioration in lung function in women than in men,[16,17] this is controversial.[18] In the management of bronchial asthma, some have reported that women are more affected by smoking than men.[19,20] However, the gender difference with regard to the influence of active smoking on asthma patients in Japan is unclear, because Japan differs in race and lifestyle from the countries where such analyses were performed.

A questionnaire survey was conducted by the Niigata Asthma Treatment Study Group, taking these factors into consideration. Subjects from this survey were adult patients with bronchial asthma who visited medical institutions in the Niigata Prefecture, starting in 1998. The attending physicians of these patients were included in the survey. Based on this survey, we have reported the clinical characteristics of adult bronchial asthma patients,[21] the characteristics of elderly bronchial asthma patients[22] and changes in asthma management.[23]

At the beginning of this survey, there were no questions about active cigarette smoking; these questions were added in 2000. In this paper, the analysis was based on results obtained from surveys conducted from 2000 onwards, to examine the relationship between asthma and active smoking, and any gender difference.

METHODS

The questionnaire used in this study was performed in Niigata Prefecture, Japan, under the Ethical Principles for Medical Research Involving Human Subjects, Declaration of Helsinki. The institutions involved were 32 large hospitals (200 beds or more), 24 small hospitals (< 200 beds) and 44 clinics (no beds). Eight thousand questionnaires were prepared and 3293 were answered (collection rate : 41.2%). The contents of the questionnaire are shown in Table 1 (originally in Japanese). The questionnaire was carried out over 2 months from September to October 2000. Subjects were recruited from adult patients (aged 16 years and over) with bronchial asthma who regularly visited the participating institutions for asthma management (typically once or twice per month). They were recruited by their physician during a regular visit during the study period. The recruited patients were asked to complete the questionnaire by themselves (Table 1). Therefore, the understanding of technical terms such as "attack" or "unconscious" (Table 1) depended upon individual patients.

For an evaluation of asthma control, patients were asked about their mean peak expiratory flow value (PEFV) and the presence of asthma attacks during the two weeks prior to the questionnaire. The patients were also asked about their asthma during the year prior to the questionnaire by choosing 1 of 3 answers: "few attacks," "seasonal attacks" or "frequent attacks." The questionnaire asked about asthma-related symptoms in the two weeks prior to the questionnaire, including cough and sputum in the morning and at night, and sleep disturbance. The questionnaire also inquired about asthma-related emergencies, including ambulance use, emergency department visits and hospitalization, and life-threatening events including unconsciousness during asthma attacks, and attacks requiring respirator management, and asthma attacks induced by anti-inflammatory-agent (aspirin induced asthma). The subjects were asked to answer "yes" or "no" to the following five questions: "Have you ever been hospitalized due to asthma?", "Have you ever been taken by ambulance or visited an emergency room due to an attack?", "Have you ever been placed on a respirator due to an asthma attack?", "Have you ever been unconscious during an asthma attack?", and "Have you ever had an attack induced by anti-inflammatory drugs including painkillers, antipyretics, or cold medicine?" To evaluate problems with asthma management and treatment related to normal activity levels, the questionnaire asked patients about satisfaction in daily life. The subjects answered by choosing 1 of 5 answers: "very satisfied," "fairly satisfied," "mediocre," "slightly unsatisfied," and "not satisfied."

At the time that the patient completed their questionnaire, their physician was asked to supply details of current treatment, the type of asthma (atopic or non-atopic, according to elevation of serum total IgE or significant detection of specific IgE for allergens), and the severity of asthma, using the adult bronchial asthma severity assessment committee's standards of the Japanese Society of Allergology. As shown in Table 2, severity was classified according to a combination of frequency and degree of attacks during the worst 4 weeks prior to the questionnaire. However, in cases of administration of corticosteroids, the total dosage of corticosteroids, including inhaled corticosteroids, can independently define the severity. A case was classified as "severe" with a dose of more

Table 3-a Background and medication in male patients

	non-smokers (*n* = 325)	current smokers (*n* = 340)
Brinkman's index (mean +/-SD)		347 +/- 192
age (mean +/-SD)	51.6 +/- 19.0	50.5 +/- 16.6
duration (year: mean +/-SD)	15.0 +/- 15.9	16.6 +/- 21.1 *
type: % (atopic/nonatopic)	64.3/29.5	70.3/22.1 *
severity: % (mild/moderate/severe)	42.8/46.2/8.3	44.1/43.5/5.0
rate of PEF use (%)	40.0	32.9
rate of ICS use (%)	70.8	59.7 * *
ICS dose (μg/day: calcuiated as BDP)	561 +/- 173	621 +/- 336
rate of OCS use (%)	10.8	10.0
OCS dose (mg/day: calculated as PSL)	6.3 +/- 2.8	7.0 +/- 3.9
rate of LTRA use (%)	36.9	33.2
rate of OSRT use (%)	80.6	74.1 *
use of SABA on demand	35.1	34.4
regular	2.2	2.1
experience of ambulance or ED (%)	36.0	32.1
experience of hospitalization (%)	41.2	37.1
experience of UC (%)	6.5	4.7
experience of RM (%)	4.6	5.3
experience of AIA (%)	6.8	6.2

ICS: inhaled corticosteroid, BDP: beclomethasone dipropionate, OCS: oral corticosteroid, PSL: prednisolone, LTRA: leukotriene receptor antagonist, OSRT: oral susrained-release theopyhlline, ED: emergency department, UC: unconsciousness due to asthma attacks, RM: respirator management, AIA: aspirin induced asthma attack * : $P < 0.05$, * * :$P < 0.01$ *vs* non-smokers

Table 3-b Background and drug medication in female patients

	non-smokers (*n* = 1132)	current smokers (*n* = 109)
Brinkman's index (mean +/- SD)		357 +/- 374
age (mean +/- SD)	57.4 +/- 15.3	44.3 +/- 16.5 * * *
duration (year: mean +/- SD)	16.6 +/- 18.2	18.5 +/- 20.7
type: % (atopic/nonatopic)	63.3/31.1	70.6/22.9
severity: % (mild/moderate/severe)	41.8/43.7/9.8	35.8/55.0/3.7 *
rate of PEF use (%)	40.5	35.8
rate of ICS use (%)	70.8	73.4 * *
ICS dose (μg/day: calcuiated as BDP)	606 +/- 353	589 +/- 259
rate of OCS use (%)	14.5	6.4 *
OCS dose (mg/day: calculated as PSL)	5.6 +/- 2.7	6.1 +/- 2.7
rate of LTRA use (%)	33.0	32.1
rate of OSRT use (%)	74.5	70.6
use of SABA on demand	29.0	31.2
regular	2.8	2.8
experience of ambulance or ED (%)	35.7	59.7 * * *
experience of hospitalization (%)	46.1	48.6
experience of UC (%)	7.1	2.8
experience of RM (%)	6.4	7.3
experience of AIA (%)	11.4	11.0

ICS: inhaled corticosteroid, BDP: belcomethasone dipropionate, OCS: oral corticosteroid, PSL: prednisolone, LTRA: leukotriene receptor antagonist, OSRT: oral susrained-release theophylline * :$P < 0.05$, * * :$P < 0.01$, * * * :$P < 0.001$ *vs* non-smokers

than 10 mg/day, and "moderate" with a dose of 5–10 mg/day, calculated for prednisolone.

Patients were classified into three groups : non-smokers (NS), ex-smokers (ES) and current smokers (CS). The CS group was mainly compared with the NS group, because of varied duration of smoking and of cessation of smoking in the ES group.

The results were expressed as arithmetic means

Table 4-a Presence of asthma attacks, peak flow values, asthma-related symptoms and sleep disturbance in male patients during the two weeks prior to questionnaire

	non-smokers (*n* = 325)	current smokers (*n* = 340)
PA (%)	32.6	40.0
PEFV (morning, mean +/- SD)	473 +/- 125 (*n* = 122)	443 +/- 139 (*n* = 98) * * *
PEFV (night, mean +/- SD)	484 +/- 128 (*n* = 117)	453 +/- 147 (*n* = 94) * * *
ARS in the morning (%)	45.5	64.4 * * *
sputa in the morning (%)	19.1	24.7 * *
cough in the morning (%)	17.5	33.5 * * *
ARS at night (%)	34.8	43.5 *
sputa at night (%)	11.7	14.4
cough at night (%)	10.8	12.9
sleep disturbance (%)	19.7	29.1 * *

PA: presence of asthma attacks, PEFV: peak flow value, ARS: asthma related symptoms * : $P < 0.05$, * * : $P < 0.01$, * * * : $P < 0.001$ *vs* non-smokers

Table 4-b Presence of asthma attacks, peak flow value, asthma-related symptoms and sleep disturbance in female patients during the two weeks prior to questionnaire

	non-smokers (*n* = 1132)	current smokers (*n* = 109)
PA (%)	33.0	36.4
PEFV (morning, mean +/- SD)	328 +/- 92 (*n* = 396)	374 +/- 83 (*n* = 35) * *
PEFV (night, mean +/- SD)	339 +/- 91 (*n* = 392)	387 +/- 81 (*n* = 34) * *
ARS in the morning (%)	52.8	57.8
sputa in the morning (%)	21.9	22.9
cough in the morning (%)	21.7	26.6
ARS at night (%)	39.8	41.3
sputa at night (%)	11.1	14.7
cough at night (%)	9.1	7.3
sleep disturbance (%)	30.5	29.4

PA: presence of asthma attacks, PEFV: peak flow value, ARS: asthma related symptoms * * : $P < 0.01$ *vs* non-smokers

Table 5-a Asthma attacks in males during the year prior to the questionnaire

	seasonal/few/frequent/not answered (%)
nonsmokers (*n* = 325)	116/134/43/32 (35.7/41.2/13.2/9.8)
current smokers (*n* = 340)	140/99/49/52 (41.2/29.1/14.4/15.3) *

* : $P < 0.05$ *vs* current smokers

Table 5-b Asthma attacks in females during the year prior to the questionnaire

	seasonal/few/frequent/not answered (%)
nonsmokers (*n* = 1132)	399/443/150/140 (31.6/41.3/14.0/13.1)
current smokers (*n* = 109)	49/38/13/9 (45.0/34.9/11.9/8.3)

(±SD) for continuous variables. A Mann-Whitney *U* test was used to test the equality of distributions of continuous variables. Differences between dichotomous variables were analyzed using the chi-square test. These tests were performed with Bonferroni's correction for the significance level. A logistic or multiple regression analysis was used to identify the factors influencing each dependent variable. All statistical analyses were performed using statistical software *Stat*View 5.0 PowerPC version (SAS Institute Inc., Cary, NC, USA), BMDP 3S (BMDP, Los Angeles, CA) and Statxact (Cytel Software Co., Cambridge, MA, USA). For all statistical analyses, a *P* value of less than 0.05 was considered to be statistically significant.

RESULTS

PATIENT BACKGROUND AND DRUG MEDICATION

Patient background and medication usage in the CS and NS groups are summarized in Table 3. In this study, 3293 patients responded. Of the male patients, 325 (22.0%) were classified as NS, 812 (57.0%) were classified as ES, and 340 (23.0%) were classified as CS. Of the female patients, 1132 (77.0%) were classified as NS, 229 (15.6%) were classified as ES and 109

Table 6-a Satisfaction in daily life in male

	very satisfied, fairly satisfied, mediocre, slightly unsatisfied, not satisfied (%)
non-smokers (*n* = 325)	45/193/48/27/5 (14.2/60.7/15.1/8.4/1.6)
current smokers (*n* = 340)	36/176/77/39/5 (11.3/55.4/24.2/12.3/1.6)*

* ; $P < 0.05$ *vs* non-smokers

Table 6-b Satisfaction in daily life in female

	very satisfied, fairly satisfied, mediocre, slightly unsatisfied, not satisfied (%)
non-smokers (*n* = 1132)	115/660/161/112/15 (14.1/59.8/14.6/10.1/1.4)
current smokers (*n* = 109)	16/51/26/12/4 (14.7/46.8/23.9/11.0/3.7)*

* ;$P < 0.05$ *vs* non-smokers

Table 7-a Variables

variables	type of variables	category
smoking	discrete	NS (0), ES (1), or CS (2)
age	continuous	
onset age of disease	continuous	
duration of disease	continuous	
peak flow monitoring	discrete	No (0) or Yes (1)
severity of disease	discrete	mild (0), moderate (1), or severe (2)
type of asthma	discrete	atopic asthma (0), non-atopic asthma (1)
use of oral sustaind-relaese theophylline	discrete	No (0) or Yes(1)
use of short-acting beta 2 agonist	discrete	No (0), as-needed (1), regular use (2)
use of oral corticosteroid	discrete	No (0) or Yes (1)
dose of inhaled steroid calculated as BDP	continuous	
use of antihistamines	discrete	No (0) or Yes (1)
use of leukotriene receptor antagonists	discrete	No (0) or Yes (1)
Brinkman's index	continuous	

Continuous variables were standardized to a mean of 0 and standard deviation of 1. CS: current smoking, ES: ex-smoking, NS: nonsmoking

Table 7-b Dependent variables

variables	category
ARS in the morning	No (0) or Yes (1)
sputa in the morning	No (0) or Yes (1)
cough in the morning	No (0) or Yes (1)
ARS at night	No (0) or Yes (1)
sputa at night	No (0) or Yes (1)
cough at night	No (0) or Yes (1)
sleep disturbance	No (0) or Yes (1)
experience of ambulance or emergency department	No (0) or Yes (1)
experience of unconsciousness due to asthma attacks	No (0) or Yes (1)
experience of respirator management	No (0) or Yes (1)
frequency of asthma attacks during a year	No (0), with seasonal episodes (1), or always (2)
number of asthma attacks in this two weeks	No (0), 1 to 2 times (1), 3 to 4 times (2), or more than 5 times (3)
severity of asthma attacks in this two weeks	No symptoms (0), wheeze only (1), symptoms were minimally troublesome (2), symptoms were severe but able to lie down (3), symptoms were so severe as toprevent a lie down (4), or symptoms were so severe as to prevent any movement (5)

ARS: asthma-related symptoms

(7.4%) were classified as CS. There was a marked difference in the distribution of active cigarette smoking between men and women. In male patients, the mean duration of asthma and the proportion of atopic asthma were significantly higher in the CS group than in the NS group, and the rate of inhaled corticosteroid (ICS) and oral sustained-release theophylline (OSRT) use was significantly lower in the CS group than in the NS group (Table 3-a). In female patients, patient age and rate of oral corticosteroid use were significantly lower in the CS group than in the NS group, and the rate of ICS use was significantly higher in the CS group than in the NS group (Table 3-b). There was a significant difference in disease severity between the CS group and the NS group in women, but not in men. There was a significantly higher prevalence of ambulance use and emergency department visits in the female CS group than in the female NS group. There was no significant difference in the Brinkman's index for men and women.

ASTHMA CONTROL

The presence of asthma attacks, PEFV, asthma-related symptoms, cough, sputum and sleep disturbance during the two weeks prior to the questionnaire, which reflect relatively short-term asthma control, are summarized in Table 4. In men, PEFV was significantly lower, both in the morning and at night, in the CS group than in the NS group (Table 4-a). In women, PEFV was significant higher in the CS group than in the NS group (Table 4-b). In men, there was a higher incidence of asthma-related symptoms in the morning and at night, sputum and cough in the morning, and sleep disturbance, in the CS group than in the NS group (Table 4-a). Such significant differences were not found in female patients (Table 4-b).

Asthma attacks during the year prior to the questionnaire are summarized in Table 5, which indicates relatively long-term asthma control. There was a significant difference in long-term asthma control between the CS group and the NS group in men, but not in women (Tables 5-a, b). A significant difference in satisfaction in daily life was found between the CS group and the NS group in both men and women (Tables 6-a, b).

MULTIPLE REGRESSION ANALYSIS AND LOGISTIC REGRESSION ANALYSIS (12 DEPENDENT VARIABLES AND 14 EXPLANATORY VARIABLES)

The results shown in Table 4 indicate that the susceptibility of asthma to active smoking may be different in men and women in our study. However, medications and background factors, which can influence control and symptoms of asthma, must be taken into consideration. Multiple regression analysis with a stepwise procedure for continuous data, and logistic regression analysis with a stepwise procedure for categorical data were performed. Table 7-a shows 14 explanatory variables, and Table 7-b shows 12 dependent variables used in this study.

Tables 8-a, b, c, d and e show the partially analyzed data. In men, active smoking contributed significantly to asthma-related symptoms in the morning (Table 8-a) and at night (Table 8-d), cough and sputum in the morning (Tables 8-b, c) and sleep disturbance (Table 8-e). By contrast, there was no relationship between smoking and these asthma symptoms in women.

DISCUSSION

This study analyzed the results of a questionnaire survey in Niigata Prefecture conducted on 2000. In this study, the male CS group had a longer duration of asthma and a higher incidence of atopic asthma, and the CS group had lower rates of medication with ICS and OSRT than the NS group (Table 3-a). This may influence asthma control - less medication in the male CS group could result in the poor control shown in Table 4-a. However, regression analysis revealed that the use of OSRT and ICS did not contribute to asthma symptoms in men, except that OSRT did contribute to asthma-related symptoms in the morning. On the other hand, active smoking significantly contributed to asthma symptoms (Table 8), indicating that the male CS group tended to manifest more asthma symptoms, including cough, sputum and sleep disturbance, than the male NS group.

As summarized in Tables 3-b and 4-b, there were also some differences between the female CS group and the female NS group. When interpreting these results, there were several problems. The female CS group was much younger, had a lower rate of mild asthma, a lower incidence of oral corticosteroid use, and a higher incidence of ICS use than the female NS group. It is well known that PEFV decreases with age ; the female CS group was significantly younger than the female NS group, and had a higher PEFV (Table 3-b). Therefore, Table 4-b may not exclude a contribution of smoking to asthma symptoms in the female CS group. However, regression analysis clearly showed no contribution of smoking to asthma symptoms in women. This apparently differs from the situation in men.

The finding of this study that there was a gender difference in susceptibility of asthma to active smoking was potentially a problem, because previous reports have showed that active smoking induced more respiratory symptoms, and a greater decrease in lung function, in women than in men.[16,17] Women with asthma have been reported to be more affected by smoking than men.[19,20] However, there are possible explanations for our result. Black male smokers have been reported to have a more marked decrease in lung function than black female smokers.[18] This

Table 8-a Regression analysis of asthma related symptoms in the morning

Gender	Parameters	β	S.E.	*p*	Exp (β)	Gender	Parameters	β	S.E.	*p*	Exp (β)
	use of OSRT	0.457	0.179	0.011	1.579		PEF	-0.413	0.136	0.002	0.662
	SABA			0.001			use of OSRT	0.351	0.158	0.027	1.420
	on demand	0.416	0.144	0.004	1.516		SABA			0.000	
	regular use	1.105	0.386	0.004	3.018		on demand	0.700	0.146	0.00	2.013
	severity (*vs*. mild)			0.046			regular use	0.730	0.383	0.056	2.076
Male	moderate	-0.009	0.148	0.953	0.991	Female	use of LTRA	0.320	0.142	0.024	1.377
	severe	0.577	0.251	0.022	1.782		intercept	-0.408	0.156	0.009	0.665
	smoking (*vs*. NS)			0.000							
	ES	0.314	0.165	0.058	1.369						
	CS	0.948	0.205	0.000	2.580						
	intercept	-0.957	0.212	0.000	0.384						

CS: current smoking, ES: ex-smoking, LTRA: leukotriene receptor antagonist, NS: nonsmoking, OSRT: oral sustained-release theophylline, SABA: short-acting beta 2 agonist

Table 8-b Regression analysis of morning sputum

Gender	Parameters	β	S.E.	*p*	Exp (β)	Gender	Parameters	β	S.E.	*p*	Exp (β)
	PEF use	-0.564	0.196	0.004	0.569		use of OSRT	0.579	0.213	0.007	1.784
	severity (*vs*. mild)			0.002			SABA			0.012	
	moderate	0.218	0.202	0.279	1.244	Female	on demand	0.427	0.167	0.011	1.532
	severe	1.026	0.297	0.001	2.790		regular use	0.763	0.400	0.056	2.145
Male	smoking (*vs*. NS)			0.007			intercept	-1.982	0.202	0.000	0.138
	ES	-0.165	0.228	0.471	0.848						
	CS	0.523	0.253	0.038	1.687						
	intercept	-1.681	0.224	0.000	0.186						

CS: current smoking, ES: ex-smoking, NS: nonsmoking, OSRT: oral sustained-release theophylline, SABA: short-acting beta 2 agonist

Table 8-c Regression analysis of morning cough

Gender	Parameters	β	S.E.	*p*	Exp (β)	Gender	Parameters	β	S.E.	*p*	Exp (β)
	severity (*vs*. mild)			0.000			use of OCS	0.624	0.208	0.003	1.866
	moderate	0.059	0.164	0.722	1.060		dose of ICS	0.161	0.076	0.034	1.174
	severe	0.914	0.243	0.000	2.494	Female	use of LTRA	0.476	0.166	0.004	1.609
	smoking (*vs*. NS)			0.013			Brinkman's index	0.154	0.073	0.035	1.166
Male	ES	-0.076	0.230	0.740	0.926		intercept	-1.613	0.108	0.000	0.199
	CS	0.476	0.233	0.041	1.609						
	Brinkman's index	0.189	0.086	0.028	1.208						
	intercept	-1.242	0.205	0.000	0.289						

CS: current smoking, ES: ex-smoking, NS: nonsmoking, ICS: inhaled corticosteroid, OCS: oral corticosteroid, LTRA: leukotriene receptor antagonist, SABA: short-acting beta 2 agonist

means that the previously reported susceptibility pattern is still controversial. Another is that these studies were performed outside Japan. Despite the high prevalence of smoking in Japan, the incidence of lung cancer has been lower in Japan than in Western countries ("the Japanese smoking paradox"),[24] indicating that the Japanese may also differ from other races in their susceptibility of asthma to active smoking. A recent study performed in Japan revealed fewer (but not significantly fewer) effects of active smoking on female smokers than male smokers ;[9] this result was similar to our own, except that our study has clearly demonstrated a significant difference in susceptibility of asthma symptoms to smoking.

In other advanced countries, the current smoking rate among asthma patients ranges from 17% to 35%, with little gender difference.[2-9] However, the current smoking rate among women in this study was lower

Table 8-d Regression analysis of asthma related symptoms at night

Gender	Parameters	β	S.E.	*p*	Exp (β)	Gender	Parameters	β	S.E.	*p*	Exp (β)
	SABA			0.003			PEF	-0.285	0.143	0.046	0.752
	on demand	0.408	0.149	0.006	1.504		use of OSRT	0.544	0.177	0.002	1.724
	regular use	0.857	0.343	0.013	2.355		SABA			0.000	
	severity (*vs*. mild)			0.005		Female	on demand	0.792	0.149	0.000	2.207
Male	moderate	0.102	0.153	0.505	1.108		regular use	0.806	0.379	0.033	2.240
	severe	0.771	0.240	0.001	2.161		use of OCS	0.499	0.193	0.010	1.647
	Smoking (*vs*. NS)			0.050			intercept	-1.294	0.176	0.000	0.274
	ES	0.104	0.176	0.554	1.110						
	CS	0.474	0.208	0.023	1.606						
	intercept	-1.143	0.178	0.000	0.319						

CS: current smoking, ES: ex-smoking, NS: nonsmoking, OCS: oral corticosteroid, OSRT: oral sustained-release theophylline, SABA: short-acting beta 2 agonist

Table 8-e Regression analysis of sleep disturbance

Gender	Parameters	β	S.E.	*p*	Exp (β)	Gender	Parameters	β	S.E.	*p*	Exp (β)
	duration of disease	0.162	0.078	0.037	1.176		PEF	-0.414	0.156	0.008	0.661
	SABA			0.000			use of OSRT	0.451	0.194	0.020	1.569
	on demand	0.649	0.170	0.000	1.914	Female	SABA			0.000	
	regular use	1.421	0.354	0.000	4.140		on demand	0.804	0.161	0.000	2.235
	Smoking (*vs*. NS)			0.001			regular use	1.391	0.379	0.000	4.020
Male	ES	0.817	0.224	0.000	2.265		intercept	-1.581	0.194	0.000	0.206
	CS	0.777	0.260	0.003	2.176						
	severity (*vs*. mild)			0.001							
	moderate	0.007	0.179	0.970	1.007						
	severe	0.921	0.257	0.000	2.512						
	intercept	-2.361	0.237	0.000	0.094						

CS: current smoking, ES: ex-smoking, NS: nonsmoking, OSRT: oral sustained-release theophylline, SABA: short-acting beta 2 agonist

than this (7.4%), although the Brinkman's Index was the same for the male and female CS groups (Table 3). Because other lifestyle factors were not examined in this study, it is uncertain whether active smoking was independent of other lifestyle factors. When classification was performed according to smoking status, unexpected selection related to other factors in the Japanese female lifestyle may occur. Table 3-b showed a significant increase in the rate of experience of ambulance or ED in female CS group compared with female NS group, which may be related with this factor associated with Japanese female lifestyle. The Japanese lifestyle is now changing toward the Western lifestyle. Therefore further investigation is required.

This gender difference can influence the management of asthma. Stopping smoking is one of the most important steps in the management of asthmatic smokers, especially in men. It has been reported that an inhaled beta2 agonist, which can immediately improve asthma symptoms, improved ICS compliance.[25] This indicates that relief of asthma symptoms may be linked to improvement of other important factors in asthma management. The weaker linkage between smoking and asthma symptoms in women than in men could give unexpected results, such as restarting smoking. When female asthmatic smokers quit smoking, it may be important to inform them that stopping smoking will not always improve asthma symptoms. Thus, a gender-specific approach to smoking cessation is needed.

In summary, a questionnaire survey of adult patients with bronchial asthma, and their attending physicians in Niigata Prefecture, Japan, was analyzed with a focus on active smoking and gender differences. In the male CS group, there were more asthma-related symptoms, such as morning sputum and cough, and more severe sleep disturbance than those in the male NS group. In the female CS group, however, these symptoms were uncommon. A logistic and multiple regression analysis confirmed these significant differences between men and women. The gender differences in susceptibility of asthma to active smoking suggest the necessity of gender-specific

strategies for smoking cessation, although further investigation is required.

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